REMARKS

Claims 1–71 are pending and under consideration. Applicants herein cancel claims 26-28, and 36-38 without prejudice, and add new claims 72-141. After entry of this amendment, pending claims will be 1–25, 29–35, 39–141.

The Examiner is kindly thanked for courtesies extended during a telephonic communication on October 1, 2003.

Amendments to the Specification

Applicants have amended the specification to correct a number of minor defects of grammar and spelling. Specifically, the spelling of "spatially", "affect", "diffract", "fits", and "hanging" on pages 5, 10, 16, 17 and 30, respectively, has been corrected, and a missing word "between" has been inserted on page 18. Additionally, indefinite article "an" has been replaced by "a" on page 18.

Applicants have also amended the specification to introduce a priority claim not present in the specification as filed when it entered the U.S. national stage from the Patent Cooperation Treaty.

None of these amendments introduce new matter, and entry thereof is respectfully requested.

Amendments to the Claims and New Claims

Independent claims 1 and 14 are amended to show various features of the atomic structural model, in particular that it contains coordinates of a coactivator molecule bound to the coactivator binding site, and coordinates of helix 12. Support for these amendments can be found in the specification as filed, for example in FIG. 2A, and in Example 3, in particular at page 42, lines 21–28. Claims 1 and 14 have also been amended to recite modeling a test compound in the singular, superseding the originally presented plural. References to specific receptor residues have been deleted from these claims. Recitation of further lists of specific residues is now found in various newly presented dependent claims, as further discussed hereinbelow.

Claims 2 and 15 have been amended to include the list of residues previously presented in claim 1, and also to include a limitation that the test compound interacts with one of the listed residues, a limitation that finds support in the specification as filed, at page 5, lines 22–25.

Claim 4 has been amended to recite features of helix 12, as found in the specification as filed at, for example, page 11, lines 11 –20.

Claims 5, 9, 23, and 47 have been amended to correct various informalities: a lack of antecedent basis of "blocking" in claim 5, and omission of an indefinite article in claims 9, 23 and 47.

Claim 10 has been amended to more particularly recite Applicants' invention.

Claim 22 has been amended to recite a property of an agonist compound and finds support in the specification as filed at, for example, page 2, lines 20–21, and at page 5, lines 17–18.

Claim 24 has been amended to recite a method of identifying an agonist of ligand binding to an estrogen receptor, and to show various features of the atomic structural model, in particular that it contains coordinates of a coactivator molecule bound to the coactivator binding site, and coordinates of helix 12. Support for these amendments can be found in the specification as filed, for example in FIG. 2A, and in Example 3, in particular at page 42, lines 21–28. Claim 24 has been further amended to delete the step of providing atomic coordinates to a computerized modelling system, a step which is now presented in claim 108. Claim 24 has also been amended to recite modeling a test compound in the singular, superseding the originally presented plural. References to specific receptor residues have been deleted from claim 24 and represented in claim 25 as amended herein.

Claim 25 has also been amended to include a limitation that the test compound binds to one of the listed residues, a limitation that finds support in the specification as filed, at page 5, lines 22–25.

Claims 26 – 28 have been cancelled without prejudice.

Claim 29 has been amended to more particularly recite that which Applicants consider to be the invention. Support for these amendments can be found in the specification as filed, for example in FIG. 2A, and in Example 3, in particular at page 42, lines 21–28, and also in the specification as filed, at page 5, lines 22–25, as well as in the claim as originally filed.

Support for the amendment to claim 30 can be found in the specification as filed at, for example, page 11, lines 11 –20.

Claim 34 has been amended to recite a machine-readable data storage medium encoded with data that comprises coordinates of an estrogen receptor ligand binding domain with various properties. Support for such an amendment can be found in the specification as filed at

Appendix 1, and for example in FIG. 2A, and in Example 3, in particular at page 42, lines 21–28. References to specific receptor residues have been deleted from claim 34 and represented in claim 35 as amended herein.

Claims 36 – 38 have been cancelled without prejudice.

Claim 39 has been amended to correct various informalities and to delete a reference to Appendix 2.

Claim 41 has been amended to correct a use of a definite article.

Claim 44 has been amended to recite a cocrystal comprising a portion of an estrogen receptor ligand binding domain to which is bound an agonist and a coactivator, support for which is found in Examples 1 – 3 of the specification as filed, at pages 35–42. Claim 44 has additionally been amended to delete a reference to the crystal structure resolution, a limitation that has been represented in claim 50 as amended herein.

Claim 49 has been amended to recite a cocrystal comprising a portion of an estrogen receptor ligand binding domain, support for which is found in Examples 1, 2 and 6 of the specification as filed, at pages 35–41, and 45–46.

Claim 51 has been amended to correct a lack of antecedent basis in the term "estrogen receptor α".

Claim 52 has been amended to more particularly recite that which Applicant considers to be the invention. Support for these amendments can be found in the specification as filed, for example in FIG. 2A, and in Example 3, in particular at page 42, lines 21–28, and also in the specification as filed, at page 5, lines 22–25, as well as in the claim as originally filed. Residues deleted from claim 52 have been represented in claim 53 as amended herein.

Claim 53 has further been amended to recite that the first chemical moiety interacts with at least one of the amino acid residues, a limitation that was originally in claim 52.

Claim 54 has been amended to conform antecedent basis in the term "chemical modification."

Claims 55 and 56 have been amended to more particularly recite that which Applicant considers to be the invention, as well as to correct various informalities of grammar, and the spelling of "van der Waals", as would be understood by one of ordinary skill in the art.

Claim 59 has been amended to correct a lack of antecedent basis in the term "estrogen receptor".

Claim 67 has been amended to more particularly recite that which Applicant considers to be the invention. Support for these amendments can be found in the specification as filed, for example in FIG. 2A, and in Example 3, in particular at page 42, lines 21–28, and also in the specification as filed, at page 5, lines 22–25, as well as in the claim as originally filed. Residues deleted from claim 67 have been represented in claim 68 as amended herein.

Claim 68 has further been amended to recite that the first chemical moiety interacts with at least one of the amino acid residues, a limitation that was originally in claim 67.

Claim 71 has been amended to more particularly recite that which Applicant considers to be the invention. In particular, fitting a model into an atomic structural model of the ligand binding domain is contemplated in the specification as filed, at page 20, lines 7–8.

Applicants further respectfully request consideration of new claims 72–141, presented herein, all of which find support in the specification as filed.

Claims 72, 86, and 121 recite methods of identifying ligands wherein a test compound is an antagonist that permits helix 12 to bind to a static region of the estrogen receptor coactivator binding site, and find support in the specification as filed at page 35, lines 6 – 9.

Claims 73, 87, 113, 127 recite methods of identifying ligands in which the atomic structural model of Appendix 1 is used, and find support in the specification as filed at Appendix I.

Claims 74, 88, 114, and 128 recite using an atomic structural model of a homolog of the structure in Appendix 1, and find support in the specification as filed at, for example, original claim 34 and at page 27, lines 14–24.

Claims 75–78, 89–92, 109, 110, 123, and 124 recite lists of specific residues, with the additional limitation that the test compound binds to at least one of the residues in question. The justification for the lists of residues is as follows. The lists in new dependent claims 75 – 78, 89–92, 109, 110, 123, and 124 reflect various aspects of agonist, and antagonist binding that are described in the Examples presented in the specification as filed. For example, the lists in claims 75, 76, 89, 90, 109 and 110 recite the residues that line the surface of each of two binding pockets to which an agonist may bind (see Example 5, pages 44–45). Similarly, the lists in claims 77, 78, 91, 92, 123 and 124 recite the residues that line the surface of each of two binding pockets to which an antagonist may bind (see Example 8, pages 47–48).

Claims 79, 94, 111, and 125, recite that the atomic structural model is experimentally derived. Such a limitation is apparent in the specification as filed, for example in Appendix I,

through the presentation of structural coordinates of an estrogen receptor ligand binding domain to which is bound a ligand and a coactivator molecule, which have been obtained through experimental protocols described in Examples 1 and 2, at pages 35–41 of the specification as filed.

Claims 80, 95, 112, and 126 recite that the atomic structural model has a resolution of at least 2.03 Å, a limitation that finds support in the specification as filed at page 26, lines 9–10.

Claims 81, 97, and 129 recite that a method of identifying an antagonist further comprises comparing a second atomic structural model with the atomic structural model of a portion of the estrogen receptor a ligand binding domain that has a coactivator bound to the coactivator binding site. Support for such a comparison is found in the specification as filed at page 32, line 31 to page 33, line 2, and at page 33, lines 22-24.

Claims 82, 98, and 130 recite that the second atomic structural model is experimentally derived. Such a limitation is apparent in the specification as filed, for example in Appendix 2, through the presentation of structural coordinates of an estrogen receptor ligand binding domain to which is bound a ligand, which have been obtained through experimental protocols described in Examples 1, 2 and 6, at pages 35–41, and 45-46 of the specification as filed.

Claims 83, 99, and 131 recite that the atomic structural model has a resolution of at least 1.90 Å, a limitation that finds support in the specification as filed at page 26, lines 4–5.

Claims 84, 100, and 132, recite methods of identifying ligands in which the atomic structural model of Appendix 2 is used, and find support in the specification as filed at Appendix 2.

Claims 85, 101 and 133 recite using an atomic structural model of a homolog of the structure in Appendix 2, and find support in the specification as filed at, for example, original claim 34 and at page 27, lines 14–24.

Claims 93, 108 and 122 recite a step of providing atomic coordinates to a computerized modelling system. In particular, Claim 108 contains a method step originally presented in claim 24 as originally filed. The step also finds support in the specification as filed at page 6, lines 17-19.

Claims 96 and 120 recite features of helix 12, as found in the specification as filed at, for example, page 11, lines 11 –20.

Claim 107 recites a method of identifying ligands wherein a test compound is an agonist that permits a coactivator molecule to bind to a static region of the estrogen receptor coactivator binding site, and finds support in the specification as filed at page 46, lines 13 – 16.

Claims 102-104, and 106 find support in originally filed claims 6-8, and 9 respectively.

Claim 105 finds support in claim 22 as amended herein, and as discussed hereinabove.

Claim 115 has been introduced to recite a method of identifying an antagonist of ligand binding to an estrogen receptor. Claim 115 finds support in originally filed claim 24, which originally recited a method of identifying an agonist *or* antagonist of ligand binding to an estrogen receptor, but which has been amended herein to recite a method of identifying an agonist.

Claim 116 recites a list of residues that was present in originally filed claim 24, and also includes a limitation that the test compound interacts with one of the listed residues, a limitation that finds support in the specification as filed, at page 5, lines 22–25.

Claims 117-119 find support in originally filed claims 6-8 respectively.

Claim 134 finds support in the specification as filed at page 23, lines 26-30, and at page 25, lines 8-11. Claim 135 finds support at page 32, line 28 to page 33, line 2.

Claims 136-139, reciting an isolated and purified protein complex find support in Example 1 of the specification as filed, at pages 35-41.

Claims 140 and 141 find support in the specification, in claim 1 as amended herein claim and 12 as originally filed. Claims 140 and 141 recite a method of identifying a ligand that modulates nuclear receptor activity, and estrogen receptor activity, respectively, comprising screening a test compound that has been previously identified by a modeling method.

Accordingly, new claims 72-141, and the amendments herein to claims 1, 2, 4, 5, 9,10, 14, 15, 22-25, 29, 30, 34, 35, 39, 41, 44, 47, 49-56, 59, 67, 68, and 71 are supported by the specification as filed, and introduce no new matter. Accordingly, their entry is respectfully requested into the file history of the instant application.

Applicants respectfully reserve the right to prosecute cancelled claims 26–28 and 36–38 in one or more continuation and divisional applications.

CONCLUSION

Applicants submit that Claims 1–25, 29-35, and 39-141 satisfy all of the criteria for patentability and are in condition for allowance. An early indication of the same is therefore kindly solicited.

The Commissioner is authorized to charge any underpayment or credit any overpayment to Pennie & Edmonds LLP Deposit Account No. 16-1150 for the appropriate amount. A copy of this sheet is attached.

Respectfully submitted,

Date: October 23, 2003

Richard G. A. Bone
Limited Recognition under 37 C.F.R. § 10.9(b)
(Copy of Certificate attached hereto)

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CERTIFICATION OF FACSIMILE TRANSMISSION UNDER 37 C.F.R. 1.8(a)

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of:	Shiau et al.	Confirmation No.:	9894
Serial No.:	09/830,693	Art Unit:	1646
Filed:	March 30, 1999 (§ 371 date: January 29, 2002)	Examiner:	Zeman, Mary
For:	METHODS AND COMPOUNDS FOR MODULATING NUCLEAR RECEPTOR ACTIVITY	Attorney Docket No:	9811-0013-999

FEE TRANSMITTAL SHEET

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

The fee required to be filed with the accompanying amendment of even date herewith concerning the above-identified application has been estimated to be $1668.00.

The claim amendment fee has been estimated as shown below:

	(Col. 1) CLAIMS REMAINING AFTER AMENDMENT		(Col. 2) HIGHEST NO. PREVIOUSLY PAID	(Col. 3) PRESENT EXTRA	☐ SMALL ENTITY RATE	ADDIT. FEE	OR	☒ OTHER THAN A SMALL ENTITY RATE	ADDIT. FEE
TOTAL	135	MINUS	71	64	x 9	$		x 18	$ 1152.00
INDEP.	16	MINUS	10	6	x 43	$		x 86	$ 516.00
☐ FIRST PRESENTATION OF MULTIPLE DEP. CLAIM						$			$ 0.00
					TOTAL	$	OR	TOTAL	$ 1668.00

Please charge the required fee to Pennie & Edmonds LLP Deposit Account No. 16-1150. A copy of this sheet is enclosed.

Date: October 23, 2003

Respectfully submitted,

Richard G. A. Bone
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Enclosure

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☐ FIRST PRESENTATION OF MULTIPLE DEP. CLAIM					$			$ 0.00
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